



PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 01-1081)**

In the Application of:

GRAF et al.

Serial No.: 09/937,103

Filing Date: July 5, 2002

**For: Use of Trehalose For Stabilizing
A Liquid Vaccine**

Examiner: Vanessa L. Ford

Group Art Unit: 1645

Confirmation No.: 4719

Mail Stop Appeal Brief- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDED APPEAL BRIEF

Dear Sir:

This Amended Appeal Brief is submitted pursuant 37 C.F.R. § 1.136, within one month. (or thirty days) from the July 11, 2006 mailing of the Notice of Non-Compliant Appeal Brief.

TABLE OF CONTENTS

I.	Real Party in Interest	3
II.	Related Appeals and Interferences	3
III.	Status of Claims.....	3
IV.	Status of Amendments	3
V.	Summary of Claimed Subject Matter	3
VI.	Grounds of Rejection to be Reviewed on Appeal.....	4
VII.	Argument.....	4
A.	The Office Erred in Rejecting Claims 9-10 and 16 as being Obvious over Samaritania in view of Sola-Penna et al. in further view of Anderson et al.	4
i.	The Office has not identified a particularized motivation to make the specifically claimed invention.....	4
ii.	The combination of the cited references does not disclose or suggest all of the claim limitations.....	7
iii.	The ordinary artisan would not have a reasonable expectation of success because the prior art teaches away from the claimed invention	8
B.	Conclusion.....	8
VIII.	CLAIMS APPENDIX	9
IX.	EVIDENCE APPENDIX.....	10
X.	RELATED PROCEEDINGS APPENDIX.....	11

I. Real Party in Interest

The real party in interest is Sanofi Pasteur S.A., the successor in interest of Aventis Pasteur, to which this invention is assigned.

II. Related Appeals and Interferences

Applicant is not aware of any related appeals or interferences.

III. Status of Claims

Claims 9-10 and 16 are pending in this application and stand rejected. Claims 2-8, 11-15, and 17 have been canceled, as explained below. These claims were finally rejected in the Office Action mailed August 30, 2006, and Applicants received an Advisory Action, mailed January 30, 2006. A Pre-Appeal Brief was mailed on February 24, 2006, along with a Notice of Appeal and Amendment. Applicants received a panel decision, mailed March 2, 2006, noting that the Pre-Appeal Brief Request for Review was improper as it was filed concurrently with an Amendment, and the rejection of the claims was maintained. This Appeal Brief is being filed within two months of the filing of the Pre-Appeal Brief Request for Review and the Notice of Appeal.

A clean set of the pending claims is attached in the Claims Appendix beginning at page 10.

IV. Status of Amendments

To reduce the number of issues for appeal, the applicants canceled composition of matter claims 2-8, 11-15, and 17 in an Amendment dated February 24, 2006. Cancellation of these claims was done without prejudice or acquiescence to the rejections. Applicants reserved the right to pursue these claims and subject matter in continuing applications.

V. Summary of Claimed Subject Matter

The presently claimed invention relates to methods of stabilizing liquid vaccines by the addition of trehalose to the vaccine compositions. P. 1, lns 37-38 and P. 2, lns 1-3. While vaccine compositions are well known in the art, various compositions intended for immunization lose their immunogenicity, and therefore their efficacy, over time. P. 1, lns 8-10, 17-18. Generally, the way to overcome this drawback is to freeze-dry the vaccine solution. P. 1, lns 19-20. However, this method is cumbersome and costly. P. 1, lns 24-25. This invention provides a liquid vaccine composition which comprises an antigen (a polysaccharide bound to a carrier protein) and further comprises trehalose. P. 1, ln 36 – P. 2, ln 3. The addition of trehalose stabilizes the vaccine, therefore allowing the immunogenicity of the conjugate to be maintained over time. P. 4, ln 33. It is therefore

more cost efficient and faster to generate. P. 2, Ins 16-18. Trehalose is a disaccharide known for its protective action in relation to proteins when they are subjected to high temperatures. P. 4, Ins 35-38.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether Claims 9-10 and 16 are unpatentable under 35 U.S.C §103(a) over Patent No. WO 96/29095 (hereinafter, "Samaritani") in view of Sola-Penna *et al.*, Stabilization against Thermal Inactivation Promoted by Sugars on Enzyme Structure and Function: Why is Trehalose More Effective than Other Sugars?; *Archives of Biochemistry and Physics*, Vol. 360, No. 1, Pgs. 10-14 (1998), (hereinafter "Sola-Penna"), further in view of U.S. Patent No. 5,097,020 (hereinafter "Anderson").

VII. Argument

With cancellation of claims 2-8, 11-15, and 17, there is only a single rejection remaining. This is the rejection of claims 9-10 and 16 under 35 U.S.C. § 103(a) as obvious over Samaritani in view of Sola-Penna *et al.* and further in view of Anderson *et al.*

Applicants respectfully assert that the Office's rejection does not meet the statutory standard required for an obviousness rejection. The reasons supporting the separate patentability of each of the above-identified issues is set forth below.

A. The Office Erred in Rejecting Claims 9-10 and 16 as being Obvious over Samaritania in view of Sola-Penna *et al.* in further view of Anderson *et al.*

Claims 9, 10 and 16 stand rejected as obvious over Samaritania in view of Sola-Penna in further view of Anderson. For the following reasons, the applicants respectfully traverse.

i. The Office has not identified a particularized motivation to make the specifically claimed invention

The applicants submit that the office has failed to establish a *prima facie* case of obviousness because, *inter alia*, the Office has failed to identify a legally sufficient suggestion or motivation to make presently claimed subject matter. As described in more detail below, the applicants maintain that the motivation/suggestion proffered by the Office is not specifically directed to the applicant's invention, and, therefore, legally insufficient.

The law requires that the suggestion or motivation be particularized, directed to the invention being claimed; a general motivation or suggestion is simply insufficient. This exact proposition was

directly addressed by the Federal Circuit in *In re Lee*, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002), where the court rejected the position that “The conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference.” The court stated:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. **The need for specificity pervades this authority.**

Id. at 1434 (citations omitted; emphasis added). See also *In re Deuel*, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995) (the prior art must suggest the particular form of the invention and how to make it; general guidance is insufficient); and *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art “that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious”).

The Office bears the burden of establishing a *prima facie* case of obviousness. *In re Fritsch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). As the Federal Circuit has explained, “[o]bviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching or suggestion to support the combination. Under section 103 teaching of references can be combined *only* if there is some suggestion or incentive to do so.” *ACS Hosp. Systems, Inc. v. Motefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984); see also *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

Accordingly, it is not enough that the references could be combined in the manner suggested by the Office. The prior art must also suggest the desirability (and thus the obviousness) of the combination. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (emphasis added); see also *Holdosh v. Block Drug Co.*, 786 F.Supp 1136, 1143 (Fed. Cir. 1986); *In re Fritsch*, 972 F.2d at 1266 (explaining that the “mere fact that the prior art may be modified in the manner suggested by the Office does not make the modification obvious unless the prior art suggested the desirability of the modification”). Thus, the Office can only meet the burden of establishing a *prima facie* case of obviousness “by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant

teachings of the references." *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). See also *In re Lee*, 277 F.3d at 1342-43 (stating that rejections under 103 must be based on evidence).

As the prior art must suggest the desirability of the combination, the proper view in making an obviousness determination is from a time just prior to the Applicant's conception of the invention. *In re Fine*, 837 F.2d at 1073. This is necessary, because "the references must be viewed without the benefit of hindsight vision afforded by the claimed invention." *Holdosh*, 786 F.2d at 1143. Using this reference point further prevents the impermissible use of the claimed invention as an instruction manual or template to piece together the teachings of the prior art in order to render the invention obvious. *In re Fritsch*, 972 F.2d at 1266.

In this case, there is no suggestion or motivation in the cited art to make the presently claimed invention. Samaritani teaches the use of a non-reducing sugar generally and sucrose specifically to enhance the stability of the protein hCG (human Chorionic Gonadotropin) and liquid formulations thereof to maintain the hormonal activity of hCG.¹ Samaritani does not provide any teachings or suggestions regarding the use of a non-reducing sugar for the stabilization of any other macromolecule. Samaritani is not concerned with, nor does it consider, the immunogenicity of hCG. More generally, Samaritani does not contemplate the use of a non-reducing sugar to maintain the immunogenicity of an antigen, generally, or a polysaccharide conjugated to a carrier protein, in particular. Samaritani is completely silent as to the effects of a non-reducing sugar on the immunogenicity of an antigen. This is not surprising as Samaritani is concerned not with immunogenicity at all but, as noted above, with maintaining the hormonal activity of hCG, only.

Sola-Penna *et al.* provides a study of trehalose as a stabilizer of "macromolecules," but the only macromolecules considered are enzymes and the stabilization studied was with respect to thermal effects on enzymatic activity. Sola-Penna, like Samaritani, is not concerned with immunogenicity. Consequently, there is no teaching or suggestion in Sola-Penna *et al.* that trehalose would stabilize immunogenicity of an antigen.

Anderson *et al.* provides no teachings regarding stabilization of the disclosed polysaccharide-protein carrier conjugates.

None of the cited art, alone or in combination teach or suggest the particular combination of trehalose with a polysaccharide-protein conjugate antigen. None recognize that trehalose can decrease the decay of immunogenicity of a polysaccharide-protein conjugate in a liquid vaccine

¹ In their last response, the applicants mistakenly asserted that Samaritani teaches the use trehalose for stabilizing hCG. Samaritani does not mention trehalose at all.

composition. Samaritani and Sola-Penna *et al.* are concerned with stabilizing hormone activity. But a polysaccharide-protein conjugate for use in liquid vaccine compositions has no such activities and is not employed for that purpose. Accordingly, any motivation supplied by Samaritani and Sola-Penna *et al.* to stabilize hormone activity would not motivate one to combine trehalose with a polysaccharide-protein conjugates in liquid vaccine compositions. Therefore, none of Samaritani, Sola-Penna *et al.*, or Anderson, alone or in combination, can provide a suggestion or motivation to combine trehalose with a polysaccharide-protein conjugate. Indeed, as the components of a liquid vaccine composition are not relied upon for their hormone activity, the motivation to use a non-reducing sugar like trehalose to stabilize hormone activity simply does not apply to a liquid vaccine composition.

In summary, the applicants respectfully submit that the Office has failed to identify in the prior art or generally available knowledge objective evidence of a particularized teaching or suggestion to make the presently claimed invention. Consequently, the Office has not made a *prima facie* case of obviousness.

ii. The combination of the cited references does not disclose or suggest all of the claim limitations

In order to establish a *prima facie* case of obviousness over a combination of references, the combination must teach or suggest all of the claim limitations. M.P.E.P. § 2143; *In re Royka*, 490 F.2d 981 (CCPA 1974). Even were Samaritani properly combinable with Sola-Penna and Anderson, the combination would still not render the presently claimed methods obvious, because they do not teach all the elements of the present claims and, therefore, one would not arrive at the presently claimed invention by combining the references.

Samaritani does not provide any teachings regarding the use of a non-reducing sugar for the stabilization of any other macromolecule beside HCG. Samaritani is not concerned with, nor does it consider, the immunogenicity of hCG. Sola-Penna, like Samaritani, is not concerned with immunogenicity. Consequently, there is no teaching in Sola-Penna *et al.* that trehalose would stabilize immunogenicity of an antigen. Furthermore, Anderson *et al.* provides no teachings regarding stabilization of the disclosed polysaccharide-protein carrier conjugates.

Accordingly, even were these references properly combinable, they would not result in the presently claimed invention.

iii. The ordinary artisan would not have a reasonable expectation of success because the prior art teaches away from the claimed invention

Furthermore, without supplying a teaching or even recognition that trehalose can stabilize the immunogenicity of a polysaccharide-protein conjugate antigen, the cited art could not have imbued the ordinary artisan with a reasonable expectation that adding trehalose to a polysaccharide-protein conjugate containing liquid vaccine composition would enhance the immunogenic stability of the polysaccharide-protein conjugate. Indeed, given that the components of liquid vaccine compositions are not relied on for enzymatic activity, none of the cited art provides any teachings that adding trehalose to a liquid vaccine composition would have any affect at all on such a composition.

B. Conclusion

In summary, the presently claimed methods cannot be obvious over Samaritani in view of Sola-Penna, in further view of Anderson, because:

1. The Office has not made a *prima facie* case of obviousness because it has not provided objective evidence that the prior art suggests or motivates the particular invention now being claimed;
2. The prior art does not teach all the elements of the present claims because neither Samaritani or Sola-Penna is concerned with or consider the immunogenicity of hCG, and Anderson *et al.* provides no teachings regarding stabilization of the disclosed polysaccharide-protein carrier conjugates.
3. The ordinary artisan would not have a reasonable expectation of success because without supplying a teaching or even recognition that trehalose can stabilize the immunogenicity of a polysaccharide-protein conjugate antigen, the cited art could not have imbued the ordinary artisan with a reasonable expectation that adding trehalose to a polysaccharide-protein conjugate containing liquid vaccine composition would enhance the immunogenic stability of the polysaccharide-protein conjugate.

Accordingly, the applicants respectfully submit that this rejection is improper.

Respectfully submitted,

Date: August 1, 2006


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VIII. CLAIMS APPENDIX

1. (canceled)

2. (canceled)

3. (canceled)

4. (canceled)

5. (canceled)

6. (canceled)

7. (canceled)

8. (canceled)

9. (Previously presented) A method of preserving the immunogenicity over time of a liquid vaccine composition comprising at least one antigen consisting of a polysaccharide bound to a carrier protein, wherein the method comprises combining in a liquid (a) trehalose and (b) the antigen to form a liquid vaccine composition, and storing the vaccine composition in the liquid state.

10. (Previously presented) The method as claimed in claim 9, wherein the quantity of trehalose to be added is between 3 and 12% by mass.

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (canceled)

16. (Previously presented) The method of claim 10, wherein the quantity of trehalose is about 5% by mass.

17. (canceled)

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.

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Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

In regard to the above identified application,

1. We are transmitting herewith the attached:
 - a) Amended Appeal Brief; and
 - b) Return Receipt Postcard.
2. With respect to fees:
 - a) No fees are due at this time.
 - b) Please charge any underpayment or credit any overpayment to our Deposit Account No. 13-2490.
3. CERTIFICATE OF MAILING UNDER 37 CFR § 1.10: The undersigned hereby certifies that this Transmittal Letter and the papers, as described in paragraph 1 hereinabove, are being deposited with the United States Postal Service with sufficient postage as "Express Mail Post Office to Addressee," addressed to: Mail Stop Appeal Brief- Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 1, 2006 under Express Mail label no. EV596652716US.

Respectfully submitted,

Date: August 1, 2006

By:

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